

REMARKS

A. STATUS OF THE CLAIMS

Claims 1-31 were originally filed in this application. In response to a Restriction Requirement dated May 31, 2001, Applicant elected Group V, corresponding to claims 1-13 and 23-31. Claims 2 and 14-22 were canceled in the Response filed on January 23, 2002. Claims 32 and 33 were added in the Amendment and Response, mailed October 1, 2002, to the Office Action dated May 1, 2002. Claim 8 was canceled without prejudice or disclaimer in the response mailed January 30, 2003. A request for continued examination was filed on March 10, 2003. New claim 34 has been added in this response. Thus, claims 1, 3-7, 9-13, 23-33 and new claim 34 are currently pending.

B. CLAIMS 1, 3-7, 9-13 AND 23-33 FULFILL THE REQUIREMENTS OF 35 U.S.C. §112, FIRST PARAGRAPH.

The Office Action mailed on May 19, 2003 rejects claims 1, 3-7, 9-13 and 23-33 under 35 U.S.C. §112, first paragraph based on the lack of disclosure enabling any person of ordinary skill in the art to use the invention commensurate with the scope of the claims. The Action states that the following aspect of the claims is not enabled: 1) reducing the number or inhibiting metastases in tissues other than lung; 2) administration of any aminoalkylphosphorothioate; 3) administration of an aminoalkylphosphorothioate at a concentration of 10 mg/kg to less than 50 mg/kg and between 100 mg/kg to 150 mg/kg; and 4) *in vivo* administration of aminoalkylphosphorothioate to an animal. Applicants respectfully traverse these rejections.

The standard for determining whether the specification meets the enablement requirement is that the claimed invention be enabled so that any person of ordinary skill in the art can make and use the invention without *undue experimentation*. *In re Wands*, 858 F.2d at 737, 8 USPQ2d

at 1404 (Fed. Cir. 1988), as cited in the MPEP at 2164.01. The initial burden is on the Examiner to establish a reasonable basis to question enablement, as provided in MPEP section 2164.04:

In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. citing *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)

As is further provided in MPEP 2164.04, it is incumbent on the Patent Office to provide acceptable evidence or reason to support a position of non-enablement. The current Action lacks sufficient *evidence* to support a determination that the disclosure does not satisfy the enablement requirement, nor does the Action provide a reasonable basis to question the enabled scope of the present claims.

1. Reducing the Number or Inhibiting Metastases in Tissues other than Lung (tissues)

The present claims are enabled for methods for reducing the number of metastases in an animal, which includes metastatic spread to a variety of organs or tissue types. In the specification, metastasis is *modeled* by using the mouse pulmonary nodule model to represent metastasis in general and should not be construed as limiting the methods to reducing metastatic spread to the lung only. Indicative of this position is the disclosure in the specification on page 13 that states:

Target cancer cells include cancers of the lung, brain, prostate, kidney, liver, ovary, breast, skin, stomach, esophagus, bone, pancreas, gum, tongue, head and neck, testicles, colon, gastrointestinal, cervix, lymphatic system and blood.

The Action supplies no evidence or reasoning why one of ordinary skill in the art would understand otherwise. It is not Applicants' burden to provide evidence or showing that such is true. The initial burden is the Examiner's to provide a *prima facie* case as to why one of ordinary skill would doubt such a contention.

The Action erroneously applies the teachings of Kanclerz *et al.* The Kanclerz *et al.* reference is irrelevant with respect to reducing the number of metastases. Kanclerz *et al.* describes experiments concerning growth of cancer cells that have already disseminated as is evident from the authors' statement in the abstract that reads "This technique results in the induction of metastatic disease in lungs and at other anatomical sites and allows the independent **treatment of disseminated tumor cells.**" (emphasis added) Their observations do not implicate the present invention because there is a fundamental distinction between 1) the mechanism of dissemination, as addressed in the present invention and 2) the growth of a cell that has already been disseminated to a tissue. Once invasion of the tissue occurs the effects of a compound would be relevant only to the regulation of growth, not to the **invasion** of the cancer cell in a distant tissue. Again, the present invention concerns the regulation of the **invasion**, not the growth of the cell post-invasion. Thus, it is clear that Kanclerz *et al.* is reporting observations related to growth control **after** the cell has invaded the tissue, and any results described cannot be compared to the present invention.

The Action also questions the exemplary methods described in the present application by stating the studies described administer WR-2721 **after** the injection of cells into the blood stream or into a muscle to establish a localized tumor in the model animal. Applicants direct the Examiner to the fact that WR-2721 was administered on the **first** day following injection of the cells. The presence of cancer cells in the blood stream or in an established tumor are needed to test the inhibition of the metastatic ability, *i.e.*, invasiveness of the cells. The injection of WR-2721 on the first day after injection of the cells is done to examine the effect of the drug on the invasive ability of the cells and in no way indicates the treatment of cells that have already invaded the tissue. In contrast, Kanclerz *et al.* injected cancer cells subcutaneously and waited

two weeks for cells to establish a tumor at the injection site and to disseminate and invade distant tissues. Twenty-hours thereafter the animals were treated. This comparison is indicative of the difference between the study of a cell invading a tissue as compared to the growth of a cell that has already invaded a tissue. Invasion of the tissue is not an immediate result of cells being injected into the blood stream of an animal.

Therefore, the Kanclerz reference has no bearing on the enablement of the present invention. Consequently, there is no evidence provided in the action that would lead one to believe that the specification would be limited to that exemplified in the working example. No evidence is provided that the pulmonary nodule assay is not indicative of metastasis generally. Applicants note again that the claims are to be considered enabled unless a *prima facie* case of non-enablement can be established. The Action lacks a *prima facie* showing of non-enablement.

2. Administration of any Aminoalkylphosphorothioate

It is clear from the specification that WR-2721 is exemplary of aminoalkylphosphorothioates. The reactive groups of the class mediate the effects seen in the example. One of ordinary skill in the art would readily recognize that aminoalkylphosphorothioate or active metabolite thereof would include the exemplary compound WR-2721 and other related compounds as described in the specification on page 13, lines 1-19. Support for this assertion can be found in issued U.S. Patent numbers 5,488,042; 5,567,686; 5,869,338; and 5,891,856, which are incorporated by reference in the instant specification on page 5, lines 16-19 and made of record in the information disclosure statement filed on September 6, 2000. The specification enables one of ordinary skill in the art to practice the invention commensurate in scope with the invention as claimed without any undue experimentation.

There is no evidence provided in the action that would lead one to believe that the specification would be limited to that exemplified in the working example. No evidence is provided that the effectiveness of WR-2721 is not indicative of aminoalkylphosphorothioates generally. Applicants note again that the claims are to be considered enabled unless a *prima facie* case of non-enablement can be established. The Action lacks a *prima facie* showing of non-enablement.

3. Aminoalkylphosphorothioate Administered at 10 mg/kg to less than 50 mg/kg and Between 100 mg/kg to 150 mg/kg

There is no relevant evidence provided in the Action that would lead one to doubt the enablement of the invention as claimed or to believe that the invention would be limited to an aminoalkylphosphorothioate dose of 50 mg/kg to 100 mg/kg, as exemplified in the working examples. Support and guidance for use of various doses of aminoalkylphosphorothioate is provided in the specification on page 6 and pages 20 to 21.

Any contention that data from the Kanclerz *et al.* and/or Milas *et al.* references contradict or would provide one of ordinary skill a basis to doubt the enablement of the present invention is erroneous. The Kanclerz *et al.* and Milas *et al.* references are irrelevant to the present invention due to the fact that the references are describing results associated with mechanisms distinct from that addressed in the present application, *i.e.*, growth of a tumor cell that has already disseminated (Kanclerz), as discussed above, and enhanced metastasis in lung tissue that has been damaged by chemicals or radiation (Milas), and not the invasion of a tumor cell (metastasis) into an undamaged tissue, as shown in the present invention. The Milas *et al.* reference has been discussed at length in previous responses with regard to cytoprotective doses and the fact that the dose of aminoalkylphosphorothioate in the present invention is a

subcytoprotective dose. In addition, Milas *et al.* describe a reduction in the enhancement of metastases that is produced upon treatments that cause damage to tissues of the treated animal. Thus, Milas *et al.* require the treatment of the animal with chemicals or radiation to induce the enhancement. The present invention has no such requirement.

The burden is on the Examiner to provide reasonable basis of non-enablement. The mere statement of such does not meet the standards set forth for demonstrating a lack of enablement. There is no requirement for the Applicants to provide a working example for each and every embodiment of the invention. Applicants point to the specification at page 6, pages 20-21, and Examples 1 and 2 that provide guidance for one of ordinary skill in the art to use the invention as claimed. Effectiveness of aminoalkylphosphorothioate at exemplary concentrations of 50 mg/kg and 100 mg/kg are shown. Dosages of aminoalkylphosphorothioate of 10 mg/kg to 50 mg/kg and 100 mg/kg to 150 mg/kg are described such that one of ordinary skill in the art could practice the invention without *undue* experimentation. As stated in the MPEP at 2164.01 “The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504 190 USPQ 214. 219 (CCPA 1976).”

There is no evidence provided in the action that would lead one to believe that the specification would be limited to that exemplified in the working example. Applicants note again that the claims are to be considered enabled unless a *prima facie* case of non-enablement can be established. The Action lacks a *prima facie* showing of non-enablement.

4. *In vivo* Administration of Aminoalkylphosphorothioate

In addressing the rejection based on the lack of enablement for *in vivo* use, the Action relies on the unsupported statement that the specification fails to provide adequate guidance and

evidence for use of the claimed invention *in vivo*. The Action also cites Gura in support of this contention. The generalities of the Gura reference provides nothing that is directly relevant to the present application. With all due respect to the author, there is nothing that establishes the author as being one of authority in the art. The references speaks to the need for improved screening methods, but does not provide any data that would bring into doubt the present invention or indicate the disregard of *in vivo* efficacy in mice. Even though current methods are not 100% in identifying a commercial drug, the FDA relies on preclinical testing in animal models. The burden is on the Examiner to provide reasoning and evidence of non-enablement. The mere statement of such does not meet the standards set forth for demonstrating a lack of enablement. Even so, Applicants point to the specification at pages 24-25 where the effectiveness of an exemplary aminoalkylphosphorothioate, as presently claimed, on multiple tumor systems is shown.

For example, Tables 1 and 2 on page 25 demonstrate the effectiveness of a single dose of 50 mg/kg of WR-2721 for various tumor types (SA-NH, Mca-K, and Oca-I). Similarly, dosage schedules of 50-100 mg/kg every other day for 6 days (page 28, line 9) and a dose 50 mg/kg every third day (pg. 23, line 18) are demonstrated. Therefore, both single dosage and multiple dose schedules are exemplified in the specification. Furthermore, pages 23-24 of the specification describe the assaying of tumors in mice and the results of those experiments are disclosed and illustrated in FIGs. 1 and 2. The *in vivo* data provided in the specification has not been rebutted by any evidence or reasoning provided in the Action or in previous Actions. The demonstration of treatment in mice is adequate enablement of the claimed invention; proof of efficacy in clinical trials involving humans is not a requirement for patentability. *See In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995). *See also Scott v. Finney*, 34 F.3d 1058, 1063, 32

U.S.P.Q.2d 1115, 1120 (Fed. Cir. 1994) ("Title 35 does not demand that such human testing occur within the confines of Patent and Trademark (PTO) proceedings."). The claims are enabled for *in vivo* use. The Applicant has taught such use in their specification. Absent any evidence to the contrary, the invention as claimed is enabled by the instant specification.

In light of the facts presented above the Action has failed to provide evidence or a factual basis for questioning the enablement of the invention as claimed. In the interest of judicious prosecution, Applicant request the reconsideration and withdrawal of the rejection.

The Examiner is invited to contact the undersigned patent agent at 713-651-5391 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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